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Schizophyllum commune sphenoidal sinusitis as presentation of a non-Hodgkin Lymphoma

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ABSTRACT

Schizophyllum commune is a basidiomycetes worldwide distributed that has emerged as cause of invasive infections in immunosuppressed patients. We present a case of a man who was simultaneously diagnosed with a small cell non-Hodgkin lymphoma and a sphenoid sinusitis by *S. commune*. Intraoperative observation and histology description were crucial to consider an alternative diagnosis to mucormycosis suggested by the MRI. The diagnosis was made based on PCR identification and sequencing.

1. Introduction

Schizophyllum commune is a basidiomycete fungi with worldwide distribution that has emerged as cause of invasive infections in immunosuppressed and, rarely, in immunocompetent patients. It is widely distributed in the environment, growing as common split gill mushroom on decaying organic matter, such as rotten wood and trees. *S. commune* has been increasingly described as etiological agent of sinusitis and less frequently as agent of other invasive infections. We report a case of *S. commune* sphenoidal sinusitis as presentation of a non-Hodgkin lymphoma in a previously healthy man.

2. Case

A 65 years-old man presented to the Emergency Department with frontal headache, fever and somnolence for 48 hours.

The patient had no relevant medical history besides recently documented lymphocytosis (44.000 lymphocytes/μL) that has not yet been investigated. This bloodwork was requested by the patients' General Practitioner for routine matters about 10 months before presentation (the patient was asymptomatic at that point). The patient lived in an urban area and worked at a shoe store. He had no contact with rural areas or animals.

When observed at the Emergency Department, he denied other neurological symptoms such as dizziness, vision changes, motor and sensibility deficits, and also respiratory, gastrointestinal and urinary symptoms. He was hemodynamically stable, presented no changes in neurological examination, and his blood work showed 59.000 lymphocytes/μL and C-Reactive Protein of 200 mg/L. Lung radiography showed a moderate left pleural effusion and the head Computerized Tomography revealed a large space occupant lesion in the sella turca/sphenoidal region with heterogenous density, not enhanced by contrast, causing expansion of the sphenoidal camera and erosion of the sellar pavement and sphenoid sinus.

Although the patient presented no respiratory failure, a thoracentesis was performed immediately revealing citric pleural effusion, 1.800 cells (98% mononuclear), with exudate characteristics. Microbiological analysis of pleural fluid was unremarkable.

Cerebral Magnetic Resonance Imaging (Fig. 1) showed a sphenoidal lesion, extending to sellar and supra-sellar region as well as posterior ethmoidal region, causing expansion of sphenoidal sinus, elevation of planum sphenoidale and bone thinning and erosion, compatible with fungal infection. The patient underwent sphenoidectomy with removal of abundant caseous content from the sphenoidal sinus; macroscopic characteristics were compatible with fungal etiology as otorhinolaryngology colleagues described finding a fungal ball when performing sphenoidectomy, and the patient was started on empirical treatment with liposomal amphotericin B 10mg/Kg/day. CSF analysis revealed

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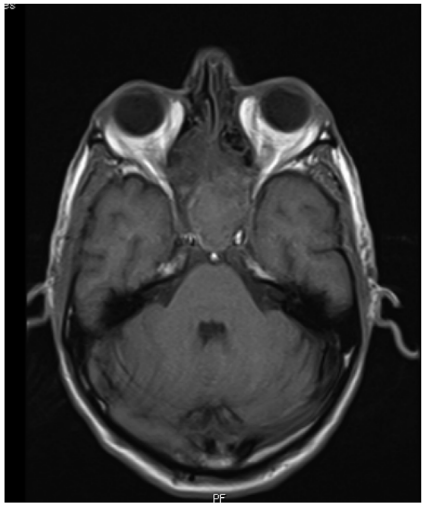

Fig. 1. Cerebral Magnetic Resonance Imaging - T1 weighted images – revealing a slightly hyperintense sphenoidal mass, with peripheral restricted diffusion and gadolinium enhance, causing expansion of sphenoidal camera and areas of bone thinning.

mild pleocytosis (predominantly lymphocytes), normal glucose and mild elevation of proteins. Cultures of the material were negative. Histologically, necroinflammatory lesions with thin and branched fungal hyphae in acute angles, with no clear septation, were identified (Fig. 2); *Mucor*, *Aspergillus* and *Fusarium* PCR were negative in the biopsied sample and in CSF. DNA was sent to the Mycology Reference Laboratory. A panfungal PCR reaction was then performed in order to detect any fungal DNA present in the sample. For that purpose, the universal fungal primers ITS1, ITS2 and ITS4 were used to amplify DNA, as described previously [1]. Amplicons were purified and sequencing was performed with the BigDye terminator v 1.1 cycle sequencing kit (Applied Biosystems).

The resultant nucleotide sequences were edited using the program Chromas Lite v 2.01 and aligned with the program CLUSTALX v 2.1 [2]. The obtained sequences were compared with sequences deposited in the GenBank (Bethesda, MD, USA) and CBS-KNAW Fungal Biodiversity Centre (Utrecht, the Netherlands) databases in order to achieve the identification of the etiological agent and the result was *Schizophyllum commune* (100% homology). The obtained sequence was deposited in GenBank with the following accession numbers MT103532 (region ITS12), MT103541 (region ITS1, 5,8s rDNA and region ITS2).

In the first week after surgery and antifungal treatment, the patient became asymptomatic.

At the same time, the patient was diagnosed with small cell non-Hodgkin Lymphoma, initiating rituximab, cyclophosphamide and prednisone at day 20 of antifungal treatment. After three weeks of amphotericin B, he initiated voriconazole 200mg bid, which he will maintain at least while he stays immunosuppressed. Therapeutic drug monitoring of voriconazole after the first and fifth months of treatment revealed therapeutic levels (between 2-6 mg/L).

A follow-up head CT 6 months after antifungal treatment shows complete resolution of inflammatory signs in the sphenoidal sinus.

3. Discussion

Basidiomycetes have been increasingly reported as cause of human infections, from allergic respiratory conditions to severe life-threatening brain lesions in both immunocompetent and immunocompromised hosts. A review on 218 reported global cases of filamentous basidiomycetes fungi infections published in 2014 found that over 50% of cases were caused by *S. commune* [3]. The majority were reported in China, Japan and India.

Clinical manifestations are diverse. Respiratory tract is involved in most cases, originating bronchopulmonary disease or sinusitis in the majority of patients [3–7]. Although not as commonly as *Aspergillus* derived cases, allergic bronchopulmonary mycosis due to *S. commune* have been described [8,9]. Other rare presentations include an epidural abscess in the middle cranial fossa (in a patient with no relevant immunosuppressive factors) [10] and cerebral abscesses [11,12]. Recently, the first case of fungemia associated with *S. commune* in an HIV patient [13] and the first case of cutaneous granuloma [14] were described. Concerning haematological malignancies, maxillary and ethmoidal sinusitis in a young woman following cord blood transplantation [15] and in a myelodysplastic syndrome patient after allogenic hematopoietic stem cell transplant were reported [16].

Typically, *S. commune* grows as white-cotton colonies and basidiocarps in culture and has some typical microscopic characteristics as connections clamps. It appears as hyaline, septate and non-dichotomously branching hyphae in direct potassium hydroxide wet mounts of clinical samples [3]. This is important to distinguish from *Aspergillus* hyphae that appear as thin, septate and branching in acute angles or Mucorales that present as large hyphae, rarely septate, and branching at right angles. In immunosuppressed patients that present chronic or acute sinusitis, these fungi might be the main differential. Sygler et al. suggest that any white, rapidly growing, sterile isolate showing good growth at 37 °C with tolerance to benomyl and susceptibility to cycloheximide should be suspected of being *S. commune* [17]. The first factor that makes *S. commune* diagnosis difficult is the lack of awareness of its existence. Also, many laboratories are unable to identify this basidiomycete, and external help to perform molecular identification may be necessary, as in our case. In a study involving 54 patients comparing culture and direct sequencing of fungi in chronic rhinosinusitis, culture allowed identification of the etiological agent in 31.5% of patients, and molecular detection followed by sequencing has identified fungal species in 81.5% of the cases (2 of which were positive

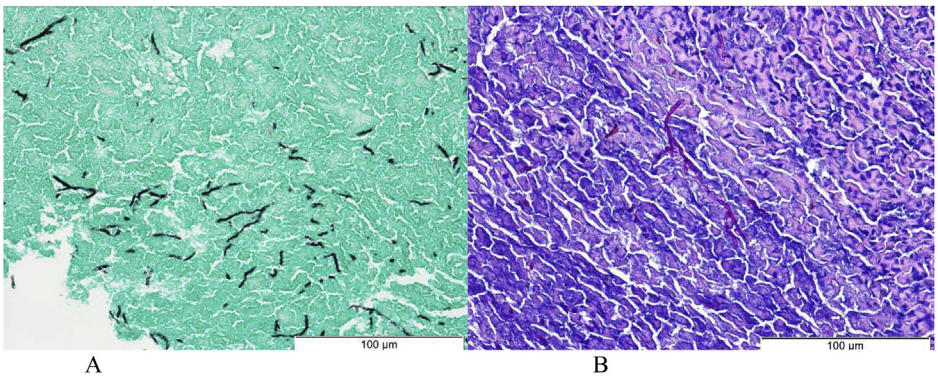

Fig. 2. Necrotic tissue with branched fungal hyphae in acute angles, with no clear septation (Fig. 2A: PAS-D - 400x; Fig. 2B: Grocott stain - 400x).

for *S. commune* in culture negative specimens) [18].

Definitive treatment strategies have not been established. Several combinations have been experimented in allergic bronchopulmonary mycosis caused by *S. commune*: itraconazole, inhaled amphotericin B plus oral or inhaled corticosteroids, and voriconazole. There is a case that did not respond to itraconazole for four months, but the patient showed a complete clinical response and no relapse after a year of voriconazole [8]. It has been demonstrated that *S. commune* has a low minimal inhibitory concentrations (MIC) to voriconazole (0,06-2 μg/mL) but high MIC to fluconazole and flucytosine (2–64 μg/mL) [19].

The absence of bone destruction by direct observation during surgery and the histology description were the first clues to consider an alternative diagnosis to mucormycosis or *Aspergillus* sinusitis, the most common etiologies of fungal sinusitis in immunosuppressed patients. On one hand, it would be expected to find bone invasion in case of mucormycosis as well as large rarely septate hyphae on histological examination. Also, no clear septation was found and PCR of *Aspergillus* was negative. Molecular detection of *S. commune* by PCR followed by sequencing were essential to establish the diagnosis. Although there are currently less than 100 cases described worldwide, this number may be underestimated and represent the absence of recognition and difficulty in identification of this species through conventional methods.

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Constent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

There are none.

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